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Treatment of cerebral ischemia or apoplexy, using N-substituted tetrahydro-pyridopyrimidinone or 1,2-benzisothiazoline-1,1-dioxide derivatives having neuroprotective activity

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Addnl. Data: STEINER G, SCHELLHAAS K, LUBISCH W, HOLZENKAMP U, STARCK D, SZABO L, EMLING F, GARCIA-LADONA F J, HOFMANN H, UNGER L

B(6-D8, 6-F3, 14-F2C, 14-F2D, 14-J1, 14-N16) .5

NOVELTY

The use of 3-(aryl-heterocyclyl-alkyl)-tetrahydro-pyridopyrimidinone or 2-(aryl-heterocyclyl-alkyl)-2,3-dihydro-1,2-benzisothiazoline-1,1-dioxide derivatives (I) for the prophylaxis and therapy of cerebral ischemia or apoplexy is new.

DETAILED DESCRIPTION

The use of tetrahydro-pyridopyrimidinone or 1,2-benzisothiazole-1,1-dioxide derivatives of formula Het-A-B-Ar (I) or their acid addition salts is claimed for the preparation of medicaments for the prophylaxis and therapy of cerebral ischemia or apoplexy.

A = 1-10C alkylene; or 2-10C alkylene containing at least one of O, S, cyclopropyl, COO, CHOH, a double bond and a triple bond;
B = 4-piperidine, 4-tetrahydro-1,2,3,6-pyridine, 4-piperazine or a corresponding group ring-expanded by one CH_2 group, bonded to A via N;
Ar = phenyl (optionally substituted by 1-4C alkyl, 1-6C alkoxy, OH, halo, CF_3, $N(R_2)_2$, $COOR_2$, CN or Ph), tetralin, indane, higher fused aromatics (e.g. naphthalene (optionally substituted by 1-4C alkyl or 1-4C alkoxy) or anthracene) or a 5- or 6-membered aromatic heterocycle (containing 1 or 2 of O and N, and optionally fused with other aromatic residues);
Het = tetrahydro-pyridopyrimidinone residue of formula (a) or 1,2-benzisothiazoline-1,1-dioxide residue of formula (b);
one of X, Y = CH_2 and the other = NR_9;
R_1, R_2 = 1-6C alkyl;
R_3, R_4 = H, 1-6C alkyl, OH, 1-6C alkoxy, halo, CF_3, NR_5R_6, $COOR_7$, NO_2, CN, pyrrole or phenyl-(1-4C) alkyl (optionally ring-substituted by halo, 1-4C alkyl, 1-4C alkoxy, CF_3, OH, NH_2, CN or NO_2);

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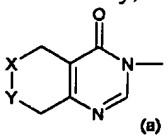
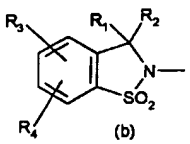
R_5, R_6 = H, 1-6C alkyl, COPh, COOtBu or 2-5C alkanoyl;
or NR_5R_6 = 5- or 6-membered ring optionally containing a second N, e.g. piperazine;
R_7 = H or 1-6C alkyl;
R_8 = H or 1-4C alkyl;
R_9 = H, 1-6C alkyl, 2-5C alkanoyl, COOtBu, aroyl or phenyl-(1-4C) alkyl (optionally ring-substituted by halo, 1-4C alkyl, 1-4C alkoxy, CF_3, OH, NH_2, CN or NO_2).


(a)


(b)

ACTIVITY

Neuroprotective; cerebroprotective; vasotropic.
No examples demonstrating biological activity are given.

MECHANISM OF ACTION

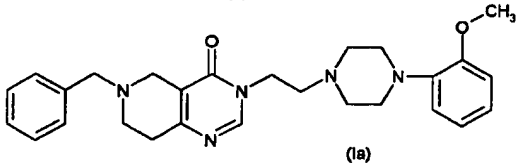
None given.

USE

For treating or preventing neurodegeneration, cerebral trauma and cerebral ischemia (especially apoplexy), and the sequelae of these diseases. (I) have neuroprotective action.

SPECIFIC COMPOUNDS

566 Compounds (I; Het = (a)) are disclosed, e.g. 3-(2-(4-(2-methoxyphenyl)-1-piperazinyl)-ethyl)-3,5,7,8-tetrahydro-4-oxo-6-benzyl-pyrido (4,3-d) pyrimidine (Ia);


(Ia)

and
639 compounds (I; Het = (b)) are disclosed, e.g. 3,3-dimethyl-2-(3-(4-tetralin-5-yl)-piperazin-1-yl)-prop-1-yl)-2,3-dihydro-1,2-benzisothiazoline-1,1-dioxide (Ib).

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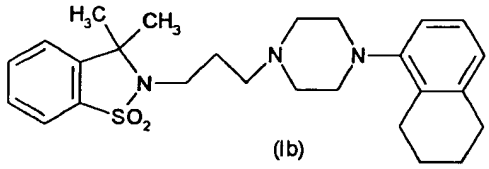
(Ib)

ADMINISTRATION

Daily dose is 1-100 mg/kg orally or 0.1-10 mg/kg parenterally.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I; Het = (a)) are described as described in DE19747063 and (I; Het = (b) are described in DE19746612.
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